=> file caplus
FILE 'CAPLUS' ENTERED AT 10:55:53 ON 27 MAY 2004
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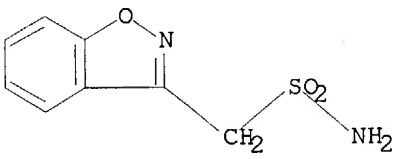
FILE COVERS 1907 - 27 May 2004 VOL 140 ISS 22
FILE LAST UPDATED: 26 May 2004 (20040526/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que
L1 STR



Structure attributes must be viewed using STN Express query preparation.
L3 18 SEA FILE=REGISTRY SSS FUL L1
L4 298 SEA FILE=CAPLUS L3
L5 1 SEA FILE=CAPLUS L4 AND DICHLOROETHANE

=> d l5 ibib abs hitstr

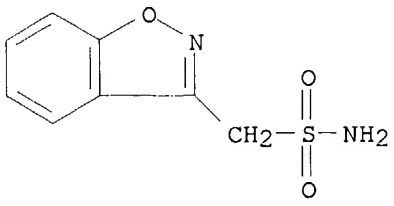
L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:55206 CAPLUS
DOCUMENT NUMBER: 114:55206
TITLE: Determination of zonisamide (3-sulfamoylmethyl-1,2-benzisoxazole) in plasma at therapeutic concentrations by high-performance liquid chromatography
AUTHOR(S): Berry, D. J.
CORPORATE SOURCE: Poisons Unit, London, SE14 5ER, UK
SOURCE: Journal of Chromatography (1990), 534, 173-81
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A selective and sensitive HPLC method for the detn. of the antiepileptic drug zonisamide in small (0.1 mL) human blood plasma samples is described. After adding the internal std. 3-sulfamoylmethyl-6-fluoro-1,2-benzisoxazole, a direct **dichloroethane** ext. of the sample is analyzed on a reversed-phase column with UV spectrophotometric detection. The method is rapid, simple, and capable of detg. plasma levels after

therapeutic ingestion of zonisamide. Some results from a dose-ranging clin. trial are presented.

IT **68291-97-4**, 1,2-Benzisoxazole-3-methanesulfonamide
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma of human, by HPLC)

RN 68291-97-4 CAPLUS

CN 1,2-Benzisoxazole-3-methanesulfonamide (9CI) (CA INDEX NAME)



=> file casreact
FILE 'CASREACT' ENTERED AT 10:58:13 ON 27 MAY 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
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FILE CONTENT:1840 - 23 May 2004 VOL 140 ISS 21

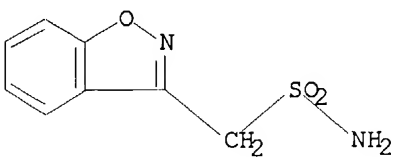
Some records from 1974 to 1991 are derived from the ZIC/VINITI data file and provided by InfoChem and some records are produced using some INPI data from the period prior to 1986.

This file contains CAS Registry Numbers for easy and accurate substance identification.

Crossover limits have been increased. See HELP RNCROSSOVER for details.

Structure search limits have been raised. See HELP SLIMIT for the new, higher limits.

=> d que
L1 STR



Structure attributes must be viewed using STN Express query preparation.
L8 5 SEA FILE=CASREACT SSS FUL L1 (28 REACTIONS)

=> d l6 1-5 ibib abs fcrd
L6 HAS NO ANSWERS

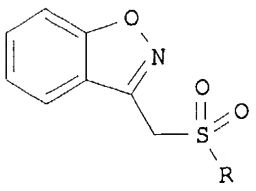
'IBIB ABS FCRD ' IS NOT A VALID STRUCTURE FORMAT KEYWORD
ENTER STRUCTURE FORMAT (SIA), SCT, SDA, SIM, SAT, NOS:end

=> d l8 1-5 ibib abs fcrd

L8 ANSWER 1 OF 5 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 139:230763 CASREACT
TITLE: Method for preparing 1,2-benzisoxazole-3-methanesulfonyl chloride using thionyl chloride, and its amidation to form zonisamide
INVENTOR(S): Mendelovici, Marioara; Gershon, Neomi; Nidam, Tamar; Pilarski, Gideon; Sterinbaum, Greta
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072552	A1	20030904	WO 2003-US5690	20030224
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004014983	A1	20040122	US 2003-373554	20030224

PRIORITY APPLN. INFO.: US 2002-358916P 20020222
OTHER SOURCE(S): MARPAT 139:230763
GI

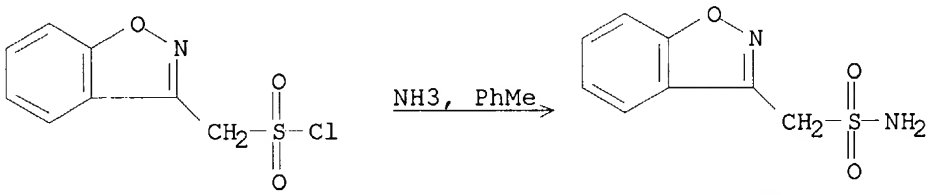


I

AB The invention relates to a process of prepg. 1,2-benzisoxazole-3-methanesulfonic acid chloride (I; R = Cl) (II). This compd. is useful as an intermediate for prepn. of the antiepileptic agent zonisamide (I; R = NH2) (III). II is prepd. via chlorination of the acid I (R = OH), or its salts or esters, using thionyl chloride (SOCl2). III is prepd. by amidation of II using NH3 in either aq., anhyd., or masked forms. More specifically, the invention provides a process of prepg. III, comprising

the steps of : (1) chlorinating I (R = OH) or its salts or esters with SOCl2 in an org. solvent and/or in the presence of a catalyst to form II; and (2) amidating II in the presence of ammonia, the latter selected from the group consisting of (i) aq. ammonia in a biphasic system, (ii) masked ammonia, and (iii) dry ammonia, to form III. Use of SOCl2 to form the acid chloride avoids the use of POCl3, which is substantially more hazardous in the workplace. For instance, 4 equiv SOCl2 was added dropwise over 3 h to a mixt. of 1 equiv I (R = OH) Na salt in PhMe contg. 0.1 equiv DMF catalyst at 50-60.degree., followed by stirring at 50.degree. for 4-5 h. Excess SOCl2 was removed by flowing N2, fresh PhMe was added, and inorg. salts were filtered to give a soln. of II in PhMe. This soln. was cooled to 10-15.degree. and anhyd. NH3(g) was bubbled through the mixt. at that temp. until the reaction was complete. by HPLC. Filtration of inorg. salts, trituration with H2O at room temp., filtration, and washing with 95% EtOH gave crude III in 91.25% yield, contg. only 2.5% I.NH3 (R = OH) (IV) as an impurity. Recrystn. from refluxing 95% with active C treatment, filtration, and slow cooling, gave III in 90.8% yield with only 0.02% IV.

RX(2) OF 3



91%

NOTE: optimization study

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 5 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 138:221579 CASREACT
TITLE: Process for the preparation of 1,2-benzisoxazole-3-methanesulfonic acid and its salts, intermediates in the synthesis of Zonisamide
INVENTOR(S): Nidam, Tamar; Mendelovici, Marioara; Schwartz, Eduard; Wizel, Shlomit
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

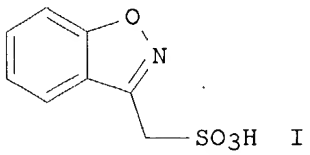
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020708	A1	20030313	WO 2002-US27593	20020829

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-316109P 20010830
US 2001-344439P 20011024

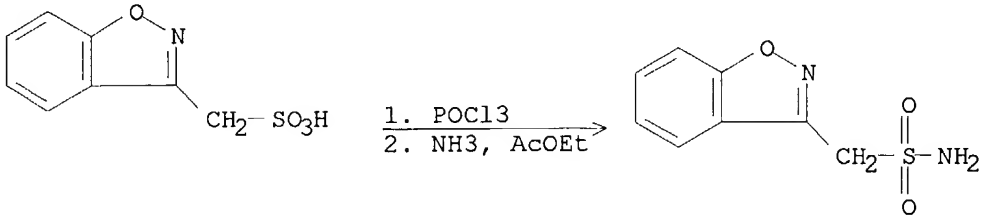
GI



I

AB A process for the prepn. of 1,2-benzisoxazole-3-methanesulfonic acid (I) by sulfonation of 1,2-benzisoxazole-3-acetic acid with chlorosulfonic acid or acyl sulfates in an org. solvent and optional conversion to its salts is disclosed. I has com. importance as a key intermediate in the prepn. of Zonisamide. For example, a soln. of 1,2-benzisoxazole-3-acetic acid (20 gm), 98% H2SO4 (22 gm), and Ac2O (23 gm) in AcOEt (80 mL) was heated at reflux for 4 h and the cooled reaction mixt. treated with aq. 10% aq. NaOH (120 mL) to give I.bul.Na (20.33 gm) in 100% purity. Advantages of the present invention are: (1) the prepn. of I without the use of dioxane, improving the environmental safety of the reaction; and (2) the increased selectivity for prepn. of the monosulfonated over the bisulfonated benzisoxazole. Cryst. forms of 1,2-benzisoxazole-3-methanesulfonic acid (BOS-H) and its salts (BOS-Na, BOS-Ca, and BOS-Ba) were also characterized.

RX(2) OF 3



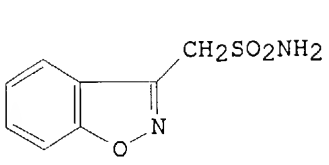
Na
(step 1)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

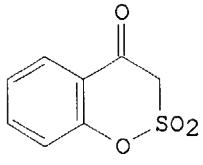
L8 ANSWER 3 OF 5 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 96:181246 CASREACT
TITLE: Studies on 3-substituted 1,2-benzisoxazole derivatives. VII. Catalytic reduction of 3-sulfamoylmethyl-1,2-benzisoxazole and reactions of the resulting products
AUTHOR(S): Uno, Hitoshi; Kurokawa, Mikio
CORPORATE SOURCE: Res. Lab., Dainippon Pharm. Co., Ltd., Suita, 564, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1982), 30(1), 333-5
CODEN: CPBTAL; ISSN: 0009-2363

10/733,565

DOCUMENT TYPE: Journal
LANGUAGE: English
GI



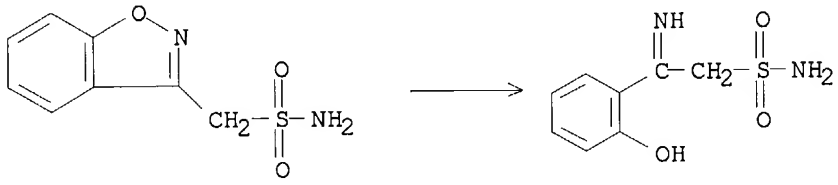
I



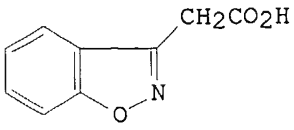
IV

AB Hydrogenation of 3-sulfamoylmethyl-1,2-benzisoxazole (I) gave 30% 2-HOC6H4C(:Z)CH2SO2NH2 (II; Z = O)(III) and 39% II (Z = NH). Treatment of III with acid gave 98% benzoxathiinone dioxide (IV). II (Z = NOH) was recyclized to give 1,2-benzisoxazole derivs. by treatment with acid or base. On pyrolysis III gave benzoxazole derivs.

RX(2) OF 9



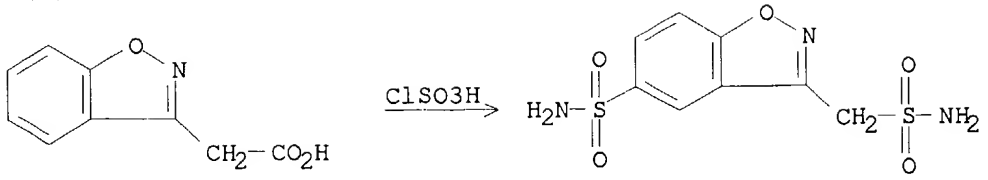
L8 ANSWER 4 OF 5 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 90:103882 CASREACT
TITLE: Studies on 3-substituted 1,2-benzisoxazole derivatives. V. Electrophilic substitutions of 1,2-benzisoxazole-3-acetic acid
AUTHOR(S): Uno, Hitoshi; Kurokawa, Mikio
CORPORATE SOURCE: Res. Lab., Dainippon Pharm. Co., Ltd., Suita, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1978), 26(11), 3498-503
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The site of the electrophilic substitution of 1,2-benzisoxazole-3-acetic acid (I) altered depending on the species of electrophiles and reaction conditions. In halogenation, only the .alpha.-methylene group of I was substituted. In chlorosulfonation, the .alpha.-methylene group was substituted at first and then the 5-position of the nucleus was substituted. In nitration, the 5-position was substituted at first and the .alpha.-methylene group was then substituted.

RX(8) OF 14



4%

L8 ANSWER 5 OF 5 CASREACT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 90:66514 CASREACT

TITLE: Studies on 3-substituted 1,2-benzisoxazole derivatives. 6. Syntheses of 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and their anticonvulsant activities

AUTHOR(S): Uno, Hitoshi; Kurokawa, Mikio; Masuda, Yoshinobu; Nishimura, Haruki

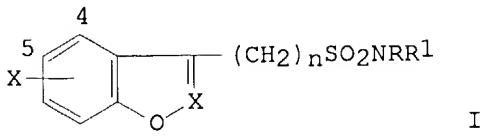
CORPORATE SOURCE: Res. Lab., Dainippon Pharm. Co., Ltd., Suita, Japan

SOURCE: Journal of Medicinal Chemistry (1979), 22(2), 180-3
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

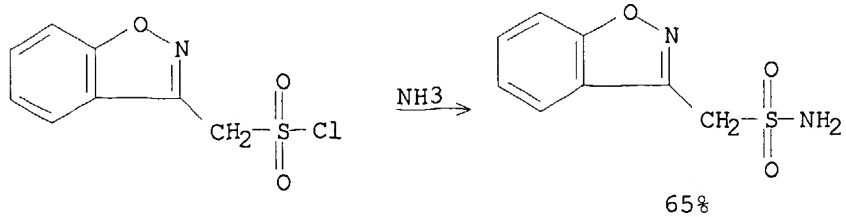
GI



I

AB Forty-three 3-(sulfamoylmethyl)-1,2-benzisoxazole [68291-97-4] derivs. I (NRR1 = NH2, NHMe, NHNH2, etc.; X = H, F, Cl, Br, etc.; n = 1, 2, or 3) were synthesized and tested for anticonvulsant activity in mice. Most of I were synthesized from 3-(bromomethyl)-1,2-benzisoxazole [37924-85-9] by reaction with Na2SO3 followed by chlorination and amination. When X = halogen at position 5 of I, increased activity and neurotoxicity was obsd. I (R = R1 = X = H, n = 1) [68291-97-4] was the most promising anticonvulsant. Structure-activity relations are discussed.

RX(1) OF 49



65%